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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,816	10/02/2003	Gordon Parry	53038AUSM1	3268

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/678,816	PARRY ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-96* is/are pending in the application.

4a) Of the above claim(s) *1-47,57,66 and 70-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-56,58-65, 67-69 and 86-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-96 are all the pending claims for this application.

2. Claims 1-47, 57, 66 and 70-85 are withdrawn, Claims 48, 60 and 63-65 are amended and new Claims 86-96 are added by amendment in the Response of 1/10/07. The amended and new claims have been considered and no new matter is added.

3. Claims 48-56, 58-65, 67-69 and 86-96 are all the claims under examination.

Objections Withdrawn

Specification

4. The objections to the specification are withdrawn as follows:

a) Pursuant to 37 CFR 1.821, Applicants have amended the specification to provide sequence identifiers for the amino acid and nucleotide sequences as indicated in the "Amendments to the Specification" (pp. 2-15) of the Response of 1/10/07.

b) The objection to the specification for omitting to include an ATCC deposit no. on p. 46, line 17 is withdrawn in view of the "Amendment to the Specification" on p. 9 of the Response of 1/10/07.

c) The objection to the improper use of trademarks (e.g., BLUESCRIPT [BLUESCRIPT®]) is withdrawn in view of the "Amendment to the Specification" on pp. 7-9 of the Response of 1/10/07.

Claims

5. The objection to Claims 63 and 67-69 is withdrawn for the following reasons:

a) Claim 63 has been amended to recite the ATCC deposit no. and further in view of Applicant's comments on p. 27 of the Response of 1/10/07.

b) Claims 67-69 have been amended to remove their dependency from non-elected claim 66, and further in view of Applicant's comments on p. 27 of the Response of 1/10/07.

Withdrawal of Rejections

Claims- 35 USC § 112, second paragraph

6. The rejection of Claim 63 for omitting to include the ATCC No. for the intended hybridoma is withdrawn in view of the amended claim and Applicant's comments p. 28 of the Response of 1/10/07.

7. The rejection of Claim 67 for reciting improper Markush group language is withdrawn in view of the amendment of the claim and further in of Applicant's comments on p. 27 of the Response of 1/10/07.

Claims - 35 USC § 102

8. The rejection of Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. 102(e) as being anticipated by Mu et al. (US20030049645) is withdrawn in view of the amendment of Claim 48 to recite that the modified hepsin molecule consists of "SEQ ID NO:9 and further in view of Applicant's comments on the top of p. 29 in the Response of

1/10/07 that "Mu et al. do not disclose generation of antibodies directed against SEQ ID NO:9."

The Examiner adds that inasmuch as independent Claims 63 and 64 are drawn to the hybridomas 14CF and 94A7, but do not recite the limitation for SEQ ID NO:9, the ability of the 14CF and 94A7 Mabs to bind the modified hepsin molecule of SEQ ID NO:9 is an inherent property of the antibodies (In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)).

9. The rejection of Claims 48-51, 53-55, 58-61, 63 and 64 under 35 U.S.C. 102(e) as being anticipated by O'Brien et al. (US20040166117) is withdrawn in view of the amendment of Claim 48 to recite that the modified hepsin molecule consists of "SEQ ID NO:9", and further in view of Applicant's comments on the bottom of p. 29 in the Response of 1/10/07 that "O'Brien et al. do not disclose generation of antibodies directed against SEQ ID NO:9."

See the Examiner's comment supra regarding the inherency of the 14C7 and 94A7 Mabs produced by the hybridomas of Claims 63 and 64 to bind the modified hepsin sequence of SEQ ID NO:9.

Claims - 35 USC § 103

10. The rejection of Claims 48-56, 58-61, 63-65 and 67-69 under 35 U.S.C. 103(a) as being unpatentable over Mu et al. (US20030049645) in view of Hellstrom et al. (USPN 5980896) is withdrawn in view of the amendment of Claim 48 to recite that the

modified hepsin molecule consists of "SEQ ID NO:9", and further in view of Applicant's comments on pp. 30-31 in the Response of 1/10/07. Applicants' allege that in general, the production of antibodies to hepsin is not obvious based on a) Applicant's PubMed search results of only five references using the terms "antibodies and hepsin" and b) the difficulty in generating anti-hepsin antibodies because of ubiquitous expression of the protein in mammals. Applicants explain that in order to produce the antibodies, hepsin-knock-out mice were immunized with the human hepsin antigen. Thus Mu neither discloses the method for producing such antibodies or the modified hepsin molecule of SEQ ID NO:9.

It is noted that Applicant's instant claims are not directed to methods for producing the claimed hybridomas, therefore the argument that Applicant's method is distinguishable from Mu's methods is irrelevant. Applicant's arguments are persuasive and the rejection over Mu and Hellstrom is withdrawn because neither Mu nor Hellstrom teach an antibody binding to the modified hepsin molecule of SEQ ID NO:9. See the Examiner's comment supra regarding the inherency of the 14C7 and 94A7 Mabs produced by the hybridomas of Claims 63 and 64 to bind the modified hepsin sequence of SEQ ID NO:9.

Rejections Maintained

Claims - 35 U.S.C. § 112, first paragraph

Biological Deposit

11. The rejection Claims 62 and 63 is maintained because Applicant's specification does not make any assurances that restrictions imposed on each of the deposits will be irrevocably removed upon the granting of a patent (see "Condition of Deposit" MPEP 2410.01).

The Examiner gratefully acknowledges Applicants' providing copies of the ATCC deposit receipts for the 14C7 and 94A7 hybridomas in addition to the ATCC deposit receipt for the non-examined DNA plasmid, pCEP4W/hepEK.

It is noted from the deposit dates for each of the hybridomas (14C7 (deposited 7/25/02); and 94A7 (deposited 9/30/03)) and the priority date for Applicant's Provisional Application No. 60/416,038 (filed 10/04/02), that only claims for the 14C7 hyrbidoma and antibody produced therefrom, would receive benefit of the priority filing date (Feldman v. Aunstrup, 517 F.2d 1351, 1355, 186 USPQ 108, 113 (CCPA 1975), cert. Denied, 424 U.S. 912 (1976)).

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 48-56, 58-61, 64, 65, 67-69 and 86-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) 48-56, 58-61, 64, 65, 67-69 and 86-96 are indefinite for the recitation "derivative thereof" because in Claim 48, it is not clear what is contemplated by a "derivative" of the antibody. The term "derivative" is not one which has a universally accepted meaning in the art not is it adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for the term. Since it unclear how the antibody is to be derived to yield the class of derivatives referred in the claims, there is no way a person of skill in the art to ascribe a discrete and identifiable class of antibodies to this term. In the absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b) Claims 61, 64, 65, 67-69 and 86-96 are indefinite because Claim 61 is drawn to "A hybridoma which produces the antibody of claim 48" because it is not clear if the claim refers to the "antibody, a fragment or derivative thereof" recited in Claim 48.

Applicant's specification does not identify any hybridomas producing recombinant forms of the hepsin-binding antibodies for fragments or derivatives thereof.

c) Claim 87 is indefinite for the recitation "is a polyclonal antibody" because the only kind of antibody that can comprise an antibody of the claim is a monoclonal antibody. Claim 87 depends from Claim 64, which is drawn to a monoclonal antibody produced by the hyrbidomas of Claims 61, 62 or 63.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 65 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising the monoclonal antibodies binding the modified hepsin molecule of SEQ ID NO:9 including 14C7 and 94A7, and using the pharmaceutical compositions for immunostaining or diagnosing hepsin protein expression in a disorder or disease, does not reasonably provide enablement for using the pharmaceutical application in any method or for just any application much less a treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claims 65 and 67-69 are drawn to pharmaceutical compositions comprising the monoclonal antibodies obtained from hybridomas 14C7 and 94A7 and from the hybridoma expressing the antibody, fragments and derivatives thereof that bind the modified hepsin molecule consisting of SEQ ID NO:9, and the composition further comprising a carrier, and further where the pharmaceutical composition is formulated as a lipsome, polymeric composition, microsphere, tablet, coated tablet or capsule. Because the claims are drawn to pharmaceutical compositions, they are examined for their intended use, and as such, the instant claims encompass an unlimited number of applications.

Disclosure in the Specification

The specification makes a general disclosure of using the antibodies to treat diseases such as cancer [0335] and for binding detecting, diagnosing, imaging and/or monitoring methodologies [0229; 0305; 0331] where hepsin protein is ordinarily expressed. The specification teaches detection methods such as immunostaining, FACs analysis and Western blotting (Examples 6-11). The specification does not provide a single example of one of the claimed antibodies in a pharmaceutical composition being used in a method of treatment for any disease much less a cancer.

Status of Immunotherapeutics/Unpredictability/Undue Experimentation

In general, the use of antibody immunotherapy for the treatment of tumors has been shown to have limitations. Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American July 1994). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Chatterjee et al state the art recognized experience that for any novel immunotherapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals, where nude mice

are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

The specification does not disclose whether the pharmaceutical compositions are effective in methods of treating a pre-existing disorder or tumor much less for inhibiting any hepsin-associated disorder, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing the use of the pharmaceutical compositions, especially the treatment of pre-existing neoplasia, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). Thus, one skilled in the art would reasonably conclude that

evidence obtained in the mouse xenograft models would necessarily correlate with results expected in human patients.

Although monoclonal antibodies have been shown to have specificity for the modified hepsin protein of SEQ ID NO:9, and monoclonal antibodies have been able to induce various degrees of tumor immunity for some diseases, not even a single example for a hepsin-associated disorder or disease much less a cancer appeared in the application (intended use) of the pharmaceutical compositions comprising the antibodies as part of an immunotherapy. Therefore, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification and the prior art to treat any subject having just any disorder with the pharmaceutical composition of the instant claims.

As evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the hepsin antibodies of the claimed pharmaceutical compositions so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

Therefore, due the unpredictability of immunotherapeutics in general, as evidenced by Jain, Chatterjee, Dermer, Gura and Seaver, and in view of the absence of

any guidance and/or working examples concerning the use the hepsin antibodies as pharmaceutical compositions, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer the pharmaceutical compositions for the treatment of any subject in need of thereof much less any hepsin-associated disease and its accompanying pathologies, including a cancer in any subject without undue experimentation.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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